THE TRANSMITTER

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Article Review

Prepared by: Mara Seier, MD, Tyler Clark, MD & Amie Hiller, MD Northwest PADRECC

Skin Nerve Misfolded α-Synuclein in Pure Autonomic Failure and Parkinson Disease:

Accumulation of misfolded α-synuclein plays a large role in the development of both pure autonomic failure (PAF) and idiopathic Parkinson's disease (iPD). There is no current consensus as to where the abnormal deposits initially accumulate in the nervous system (central vs peripheral vs autonomic), however recent findings have demonstrated the presence of α-synuclein in skin nerves in patients with early PAF and iPD. The authors of this study aimed to define the expression in skin nerves of native (n-syn) and phosphorylated (p-syn) synuclein, in iPD and PAF, and to define their use as potential biomarkers for the aforementioned conditions. This study recruited 30 patients with a suspected synucleinopathy (16 meeting diagnostic criteria for iPD and 14 meeting diagnostic criteria for PAF). These patients were compared to 15 age-matched controls. All patients underwent a work-up to exclude predisposing causes for peripheral neuropathy as well as an EMG to ensure normal large fiber nerve conduction. Selected patients then underwent 3mm punch biopsies from proximal (cervical) and distal (thigh and leg) sites to study both small nerve fiber and intraneural n-syn and p-syn. In both PAF and iPD, there was length dependent (distal, but not proximal) somatic and autonomic small fiber nerve loss that did not correlate with age or disease duration. This was not seen in controls. There was no difference in expression of n-syn between patients from both the iPD/PAF groups and the control group. There was no p-syn found in any sample taken from the control group, but p-syn was found in all patients with iPD and PAF (no correlation with age or disease duration). In PAF, there was no difference in expression between proximal and distal sites, there was a 100% concordance in expression between nearby sample sites and p-syn was found to be homogenously distributed around the muscle arrector pilorum (MAP) (40%), sweat glands (SG) (52%), arterioles (51%) and dermal nerve bundles (42%). Interestingly, in iPD, p-syn had a more proximal distribution (cervical: 100%, thigh: 75%, leg: 31%), an irregular skin distribution (nearby skin samples were not always concordantly positive) and a different distribution when compared to PAF ((MAP) (0%), sweat glands (SG) (4%), arterioles (18%) and dermal nerve bundles (19%)). This study concludes that intraneural p-syn is a sensitive and reliable in-vivo marker for PAF and iPD and that due to the different distribution, there is a different pathophysiologic mechanism driving each disorder. If used, the site chosen for biopsy will be more important in iPD than in PAF due to the aforementioned differences in distribution of p-syn between the two disorders.

Annals of Neurology. February 2016. Volume 79, Issue 2. 307-316.

Nursing home and end-of-life care in Parkinson's disease (PD)

The authors believe that end-of-life care is an integral part of neurology training and feel a neurologist's care may be beneficial in regard to an out-of-hospital death via the use of hospice services. They also were interested in looking at long term care facility (LTCF) utilization among persons with PD of different races and sexes. This is a retrospective cohort study using Medicare data from 2002-2005. They determined who had a PD diagnosis and who had seen a neurologist for at least two visits. They looked at two questions 1) who was in a residential facility and 2) who utilized hospice services the calendar year prior to death. They identified 469,055 Medicare beneficiaries over age 64 who had a diagnosis of PD. Twenty-four percent (113,668) had claims

consistent with residence in a LTCF. Those in LTCF were older and more often female – with demographics similar to non-PD LTCF population. Relative to the LTCF population without PD, African Americans with PD were over represented and Hispanic individuals with PD were under represented. Clinically a greater comorbid disease burden, a diagnosis of dementia, and a recent hip fracture increased the likely hood of being in a LTCF. They hypothesis that the higher rates of co-morbid conditions in African Americans with PD may be the driving force of greater utilization of LTCF. Since in their research "tipping points" for LTCF placement seemed to be dementia and hip fractures; they felt that focusing on the prevention of falls and hip fractures might have a particularly beneficial effect to reduce need for a LTCF, but felt more research was needed to confirm this. Only 33% of persons with PD in a LTCF had outpatient neurological care. A little over half of persons with PD who died in LTCF utilized hospice services and the rates were similar in whites, African Americans, and Hispanics but lower in Asian individuals. Persons with neurological care were 20% more likely to receive hospice care. They feel this research supports that neurological care may improve the dying process of persons with PD.

Neurology April 6, 2015 vol. 84 no. 14 Supplement S36.

Rivastigmine for gait instability in patients with Parkinson's disease (ReSPonD): a randomized, double-blind, placebo-controlled, phase 2 trial

Falls are a common complication in patients with Parkinson's disease (PD) and have been associated with an increase in gait variability. An underlying loss of cholinergic function is thought to contribute to cognitive dysfunction as well as gait changes in PD. The authors of this study aimed to assess whether treatment with the acetylcholinesterase inhibitor rivastigmine would reduce gait variability, a marker for falls, in non-demented PD patients who experienced a fall in the past year. In this phase 2 trial 130 patients were randomly assigned (1:1 ratio) to receive either 12 mg per day of rivastigmine or placebo. Both investigators and patients were masked to assignment. Primary outcome was difference in step time variability, as measured by triaxial accelerometer, between the two groups at 32-week follow-up. Gait was assessed at baseline and 32-week visit in three different conditions: normal walking, simple dual task with phonemic verbal fluency and complex dual task switching with phonemic verbal fluency. Step time variability was statistically improved in both the normal walking task (28% lower) and simple dual task (21% lower) in those taking rivastigmine compared to placebo. There was a 19% improvement in step time variability in the rivastigmine group during complex dual task that was not significant. Rate of falls per month, a secondary outcome, were reduced 45% in the rivastigmine group when adjusted for confounders. Gastrointestinal side effects (including nausea, vomiting, diarrhea) were significantly more common in rivastigmine group (52%) compared to placebo (18%). The authors conclude that rivastigmine improves gait stability and may reduce frequency of falls but a larger phase 3 study, with falls as primary outcome, is needed to confirm findings.

Lancet Neurology, March 2016, Volume 15, Issue 15, pages 249-58

Committee Activities

Clinical Care Committee

- **Rotation of Committee Chair:** Leadership for the clinical care committee rotates amongst the PADRECCs. The San Francisco PADRECC leads the committee for March/April. The committee meets via conference call the first Tuesday of the month at 12pm (EST)

- **Standardize and Optimize Clinical Care**: The committee continues to discuss a variety of clinical issues to improve patient care and outcomes. The focus is to provide clinical support to the consortium network by focusing on measures to standardize clinical care across the PADRECC network. Recent agenda items have included discussion on:

1. New treatment options for Parkinson's Disease including DUOPA™ (carbidopa and levodopa) enteral suspension delivered directly into the small intestine for the treatment of motor fluctuations for people with advanced Parkinson's disease and Rytary (carbidopa/levodopa IR/Sa combination oral medication). Discussions focused on development of standardized protocol for this therapy across the PADRECC network, logistical issues, education and support aspects.
2. Current practice regarding the use of various Neurotoxins across the PADRECC network with the objective to improve this specialized clinical practice and develop neurotoxin selection criteria for various conditions in the Veteran population.
3. Practical aspects regarding the use of DAT scans; applications and pitfalls, including the issue of drug interference
4. Palliative Care: Review of palliative care resources and practices in the PADRECCs
5. Veteran's Choice Program: optimization of care across the PADRECC network
6. Consortium Sites: How each PADRECC center can better interact with their local consortium sites.
7. National Consortium Meeting in September: tentatively scheduled for Sept 19th, 2016, one day ahead of WPC in Portland. Seeking submissions of posters (need not be original.)
8. New MRI body scanning protocols for DBS implanted patients
9. New clinical entities on the horizon: pimavanserin (Nuplazid), in process of approval by May 1st.

- **PADRECC Transmitter:** PADRECC clinicians provide reviews of recent movement disorder publications that are included in the PADRECC Transmitter

Education Committee

- **PADRECC/EES Movement Disorder Series:** The 3rd audioconference for FY 2016 was held on **March 10, 2016** *"The Role of Duopa in the Management of Parkinson's Disease"* by Dr. Ramon L. Rodriguez-Cruz-Chief of Neurology, Orlando VAMC. The audioconferences are archived on the National website *www.parkinsons.va.gov* under the Movement Disorder Series tab. Please see the **Dates to Remember** section below for a listing of upcoming FY 16 audio conferences.

- **National Newsletter:** Currently accepting articles for the **2016 VA Parkinson Report**. Topics for consideration: education, telemedicine, speech, DBS, support groups, activities, and research by the PADRECC's and their consortium members. If you are interested in submitting an article for the newsletter please email Glennys Asselin-Cavey (Glennys.Asselin@va.gov) and Suzanne Moore (Suzanne.Moore@va.gov). Articles are due by **April 29, 2016**.

- **"Mood Disorders in PD: What's New":** This enduring material project was done in collaboration with EES and is an on-line TMS self-study program that offers CME credit for a 3 year period. This program provides VHA healthcare professionals with a broadened medical awareness of Mood Disorders in PD**.** The program is **NOW** available on TMS:

  https://www.tms.va.gov/learning/user/deeplink_redirect.jsp?linkId=ITEM_DETAILS&componentID=14771&componentTypeID=VA&revisionDate=1343926380000

- **National Website Maintenance:** The committee performs monthly maintenance checks of the National Website to ensure information is current and up-to-date.

- **PADRECC Transmitter:** The committee continues to assemble and distribute this e-newsletter every other month.

Dates to Remember

April 15-21, 2016

2016 American Academy of Neurology (AAN) Meeting

Vancouver, Canada

www.ann.com

May 12th, 2016

EES/PADRECC Movement Disorders Series

Topic: Complementary and Alternative Medicine

http://www.parkinsons.va.gov/

June 19-23, 2016

2016 Movement Disorder Society International Congress

Berlin, Germany

www.mdsccongress2016.org

September 8th, 2016

EES/PADRECC Movement Disorders Series

Topic: Palliative Care and PD

http://www.parkinsons.va.gov/

September 19th, 2016 (*tentative*)

National VA PD Consortium Conference

Portland, Oregon

Additional information to follow

September 20-23, 2016

4th World Parkinson Congress

Portland, Oregon

http://www.wpc2016.org/